PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A prospective single-center clinical observational study on electronically monitored medication non-adherence, its psychosocial risk factors and lifestyle behaviors after heart transplantation – A study protocol
AUTHORS	Lieb, Marietta; Weyand, Michael; Seidl, Margot; Erim, Yesim

VERSION 1 – REVIEW

REVIEWER	Villeneuve, Claire Limoges University Hospital
REVIEW RETURNED	07-Apr-2020

GENERAL COMMENTS	General Comments: Thank you for the opportunity to review this manuscript. Improve the knowledge about psychosocial risk factors and lifestyle behaviors which could impact adherence in Heart Transplant patient is crucial. Non-adherence to immunosuppressive medication and to recommended lifestyle behaviors is known to increase the risk of rejection and comorbidities. The identification of psychosocial and behaviors l risk factors may provide recommendations and systemic changes for patients and for the health community. Abstract Will the IS trough levels be collected at each schedule visit with the cardiologist or only at T0? Introduction Line 51, the bibliography should be improved and actualized (for exemple Bertram A et al. PLoS One. 2019 - De Geest S- Transpl Int - 2014 - Villeneuve C et al Patient Educ Couns. 2019 - Paterson TSE et al. PLoS One. 2018. Line 60, the sentence “Despite their susceptibility to errors, self-reports are considered practical and inexpensive tools for NA assessment” is a bit surprising. Is it really a problem of error or just their psychometric properties which are not efficient, lack of reliability, accuracy or sensitivity? Line 63-64, some authors did not find any association between NA and trough levels (in renal transplant patients) J. Scheel J et al. BMC Nephrol.20 18 - Villeneuve C et al Patient Educ Couns. 2019. Do you think it could be the same in heart transplantation?

	Line 102-107, the aims of the study are numerous. Does the statistic analysis have taken into account this fact in the sample size calculation and the level of significance of the statistic tests to correctly conclude. Methods Line122, a minimum of 6 month after transplantation is a inclusion criteria, is there a maximum? The range could have a impact on Non-adherence. Some authors reported that patients who were adherent the first 6 month could became non-adherent after… In the measurement methods, is it possible to indicate when is assessed each measure (collateral repot, self report, trough level, electronic monitoring and psychosocial variables, non-pharmacological non-Adherence and lifestyle behavior). The figure 1 explains that but it is a bit too small. You can also referenced the figure 1 in the paragraphs. Perhaps that the paragraph line 173 could be place at the beginning to explain the chronology. Line 151, could you precise which target was define for each IS trough level? Line 191, there is numerous analysis, did the statistic methods used take this in consideration?

REVIEWER	Sabina De Geest UNiBAS & KU Leuven
REVIEW RETURNED	24-Apr-2020

GENERAL COMMENTS	A Prospective Single-Center Study on Electronically Monitored Medication Non-Adherence, Psychosocial Risk Factors and Lifestyle Behaviors after Heart Transplantation – A Study Protocol Lieb et al. 2020 This manuscript describes a single center study protocol for a prospective cohort study in adult heart transplant recipients, at least 6 months posttransplant and taking a variety of immunosuppressive regimens. The authors aim at assessing medication adherence and different non-pharmacological health behaviors in this population. Risk factors for these behaviors will be assessed. Concordance of multiple measurement for medication adherence will be evaluated (i.e self-report, physician's collateral report, IS trough levels and electronic monitoring. The manuscript was reviewed by using the SPIRIT 2013 Checklist and the EMERGE guidelines. Title - The title should best include reference to the design applied and review paper carefully in view of information requested in SPIRIT and EMERGE guidelines. Problem statement - The authors indicate this is the first study assessing HTx medication non-adherence using electronic monitoring. At least 2 papers have evaluated magnitude of non/adherence as well as risk factors using different assessment methods before: De Geest et al. 1998; De Bleser et al, 2011. - Recent meta-analyses summarizing the evidence on correlates and outcomes of smoking (Duerinckx et al. 2016), physical activity (Berben et al. 2019) and alcohol (Dobbels et al. 2019) behaviour in solid organ transplant recipients provide a basis to position the

	current study. Can the authors indicate which gap they address given the published work so far? - Schäfer-Keller et al 2008 & De Bleser et al al. 2011 have assessed medication adherence measurement methods (i.e. self-report, assay, collateral report & electronic monitoring) for immunosuppressive regimens. The current study is best positioned taking this work also into consideration the insights gained from these studies. - Has a theoretical framework been used to guide the choice of the risk factors (see EMERGE guidelines)? The authors do not assess multilevel risk factors although increasing evidence points at the role that health care worker , heart transplant center and health care system factors play in medication adherence in heart transplantation as well as in other chronically ill patient populations (Berben et al 2012; Denhaerynck et al 2018). - The range of magnitude of NA in the background needs comment that this range is influenced by variability in measurement methods, operational definitions and case finding methods. Methods - A sample of 50 heart transplant recipients will be included with varying post-transplant follow-up. Given the large number of variables included (>25), the power for data analysis will be limited. Will it be possible to reach the aims of this prospective cohort given this major limitation. - The operational definitions of medication adherence need to be reported for each medication adherence measurement and related analysis methods need to be specified. - The expected response rate of 50% seems very low taking other numbers for similar studies into consideration. - The most recent BAASIS version does not include the VAS scale as this part of the questionnaire is conceptually not appropriate (initiation/implementation/persistence) and also did not perform well in psychometric analysis. The VAS scale is therefore not recommended. - More details on the use of assay as adherence measure in light of the various immunosuppressive regimens used should be given. Operational definition and analysis methods for different regimens and combination of these different methods should be given. - Especially for electronic monitoring limited information is provided and the investigators are encouraged to used state of the art methods for EM analysis. How will you deal with different dosing regimens to determine operational definitions and how will you analyse your data? - The data analysis section is best expanded taking into consideration the feedback listed above. Discussion - Novelty of study is questioned. See comments and references above. The authors are encouraged to do a careful literature review and to argue how their single center study limited to 50 subjects can close a gap in the literature. Ethics and dissemination, Appendices - There is no information, whether the patient data will be treated anonymous / pseudonymized and who will have access to the data. This should be added. - Informed consent material is missing and should be attached in the appendix.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Claire Villeneuve):

Abstract

Reviewer:
Will the IS trough level be collected at each schedule visit with the cardiologist or only at T0?
Author's Note:
Thank you for your interest. As we have displayed in line 172, IS levels are routinely checked and registered at each follow-up examination, as well as at their resident doctors every 8-10 weeks. We only will use the IS trough level that is measured at study enrollment (T0) as well as up to three antecedent measures, since the study design (3 months duration) does not allow for a larger number of IS trough level measures. Not enough IS measures would be attained to calculate IS trough level variability (> 3 measures) during study course. No additional IS trough level checks for patients are intended, since the intervention effect should be kept to a minimum.

Introduction

Reviewer:
Line 51, the bibliography should be improved and actualized (for exemple Bertram A et al. PLoS One. 2019 - De Geest S- Transpl Int - 2014 - Villeneuve C et al Patient Educ Couns. 2019 - Paterson TSE et al. PLoS One. 2018.
Author's Note:
Thank you for your recommendation. We added the proposed literature at the respective spot.

Reviewer:
Line 60, the sentence "Despite their susceptibility to errors, self-reports are considered practical and inexpensive tools for NA assessment" is a bit surprising. Is it really a problem of error or just their psychometric properties which are not efficient, lack of reliability, accuracy or sensitivity?
Author's Note:
Thanks for this thorough review. E.g. BAASIS is a frequently used and validated self-report questionnaire for NA with good psychometric properties (Dobbels et al. 2010). However, literature suggests that inaccuracy of most of the self-report questionnaires on NA derives from social desirability and memory bias (Foster&Pai 2014, Osterberg 2007, Nevins et al., 2017). As you already mentioned, this results in a decreased sensitivity, since it overestimates adherence. This is why the search for adequate instruments is crucial. We included the error sources such as memory bias and social desirability in the respective text passage as well as the corresponding literature for better understanding (line 62).

Reviewer:
Line 63-64, some authors did not find any association between NA and trough levels (in renal transplant patients) J. Scheel J et al. BMC Nephrol.20 18 - Villeneuve C et al Patient Educ Couns. 2019. Do you think it could be the same in heart transplantation?
Author's Note:
Indeed it is possible that self-reported NA and electronically monitored NA does not coincide with IS trough levels. It often is speculated that these measurement methods act as a partial indicator for NA and depict different facets thereof (Scheel et al.2017, Schäfer-Keller et al., 2008).
Reviewer:
Line 102-107, the aims of the study are numerous. Does the statistic analysis have taken into account this fact in the sample size calculation and the level of significance of the statistic tests to correctly conclude.

Author's Note:
Thank you for your concern. We are aware that unfortunately our sample is limited, however, it should suffice for our specific research questions.
Our first research questions mostly will be investigated by applying correlational analyses as well as linear regressions which do not require a certain sample size and subsequently no power analyses. For the first RQ we are only interested in the measurement methods as potential predictors for EM, which limits the number of independent variables applied to 3 (max.5 as age and gender is controlled for). For the second RQ, we must use preliminary analyses in order to insert only the variables that are significantly correlated with the outcome. For RQ 3 we will only have the 6 variables measuring lifestyle behaviors, which again limits the number of factors inserted in the calculation. Bonferroni holm adjustments will be made for all statistical tests to correct for the alpha-error of multiple testing.

Methods

Reviewer:
Line122, a minimum of 6 month after transplantation is a inclusion criteria, is there a maximum? The range could have a impact on Non-adherence. Some authors reported that patients who were adherent the first 6 month could became non-adherent after…
Author's Note:
Thank you for this comment. As you stated the first six months can be crucial, but also quite variable in respect to adherence. Therefore we excluded this time. We deliberately did not include a maximum for time since transplantation, since most literature is controversial on how adherence behavior develops over time. Some research found that adherence is getting better (Liu et al., 2015), whereas others declare it's getting worse (Nevins et al., 2009; Jindal et al., 2009; Massey et al., 2013; De Geest et al., 2014). Until now, there is no scientifically sound criterion for a maximum at which adherence stabilizes or changes. So in order to capture the whole spectrum of adherence behavior in a cross sectional cohort, we decided not to set a maximum. If preliminary analyses display great differences in adherence depending on time since transplantation. We will control this for in the subsequent analyses.

Reviewer:
In the measurement methods, is it possible to indicate when is assessed each measure (collateral repot, self report, trough level, electronic monitoring and psychosocial variables, non-pharmacological non-Adherence and lifestyle behavior).
The figure 1 explains that but it is a bit too small. You can also referenced the figure 1 in the paragraphs. Perhaps that the paragraph line 173 could be place at the beginning to explain the chronology.
Author's Note:
As recommended we placed the section "Study Design and Measurement Points" above the section "Measurement Methods" in order to clarify the chronology of the study. We further indicated the applied measures not only in the figure but also in the text for better understanding (line 146). We shortened the sentence in line 102 to avoid redundancy.

Reviewer:
Line 151, could you precise which target was define for each IS trough level?
Author's Note:
The target levels are set by the treating physician and can vary from patient to patient, depending on the clinical course and time since transplantation. However, there are standardized graded target levels for the different immunosuppressive regimens. We have added a file in the attachment which displays these values.

In line 178 we also added that it is dependent on “time since transplantation”. I hope this explanation is in your interest.

Reviewer:
Line 191, there is numerous analysis, did the statistic methods used take this in consideration?
Author’s Note:
Thank you for your note. Almost all planned analyses are covered by the statistical methods depicted in section “Statistical Analysis Plan”:
For research question one, we plan to use Cohen’s kappa and the Intraclass Correlation Coefficient (ICC), linear regressions with the electronic monitoring as the outcome as well as linear mixed models to examine changes of adherence over time (analogous to our previous study on renal transplant recipients: Lieb et al., 2020). For the second research question, linear regression analyses will be used as well, with electronic monitoring as outcome. The third research questions will be examined by applying t-tests and cohen’s kappa.
For the assessment of potential risk factors for non-pharmacological adherence, we added the use of “logistic regression analysis” in line 224.

Reviewer 2 (Sabina DeGeest):

Title

Reviewer:
The title should best include reference to the design applied and review paper carefully in view of information requested in SPIRIT and EMERGE guidelines.
Author’s Note:
We adapted the title and included a few more information that allude to the design of the study: We included “clinical observational” and “its psychosocial risk factors” so that it is more clear that psychosocial risk factors are not assessed prospectively. I hope this is in your interest. However, we are open for further corrections.
Problem Statement:

Reviewer:
The authors indicate this is the first study assessing HTx medication non-adherence using electronic monitoring. At least 2 papers have evaluated magnitude of non/adherence as well as risk factors using different assessment methods before: De Geest et al. 1998; De Bleser et al, 2011.
Author’s Note:
Indeed electronic monitoring has been used in heart transplant recipients before, however very sparsely. As suggested we included the given literature (line 65, 70) to avoid misunderstandings. We also agree that there are studies that used a variety of measurement instruments for risk factors for non-adherence, as we have depicted starting in line 95. In line 104 we have explained that most studies apply self-reports, collateral reports and trough levels for these purposes. Although, to our knowledge, there is none that has examined the interested psychosocial factors of our study with electronic monitoring. I hope this is in your interest and you can agree with our ideas.

Reviewer:
Recent meta-analyses summarizing the evidence on correlates and outcomes of smoking (Duerinckx et al. 2016), physical activity (Berben et al. 2019) and alcohol (Dobbels et al. 2019) behaviour in solid organ transplant recipients provide a basis to position the current study. Can the authors indicate which gap they address given the published work so far?
Author’s Note:

Thank you for the literature recommendation. We included the relevant literature into the background of our manuscript (line 86 to 93). The gap we would like to address is that lifestyle behaviors have not yet been linked to electronically monitored immunosuppressive non-adherence in HTRs yet. Further, we assess certain risk factors such as self-efficacy or attachment that have not been linked to unhealthy lifestyle behaviors before, especially not in HTRs, which we have outlined in line 94 and 105.

Reviewer:
Schäfer-Keller et al 2008 & De Bleser et al al. 2011 have assessed medication adherence measurement methods (i.e. self-report, assay, collateral report & electronic monitoring) for immunosuppressive regimens. The current study is best positioned taking this work also into consideration the insights gained from these studies.
Author's Note:
As suggested we included the proposed literature in our background (line 65-70). We also mentioned the combined use of measurement methods as is done by De Bleser et al. 2011.

Reviewer:
Has a theoretical framework been used to guide the choice of the risk factors (see EMERGE guidelines)? The authors do not assess multilevel risk factors although increasing evidence points at the role that health care worker , heart transplant center and health care system factors play in medication adherence in heart transplantation as well as in other chronically ill patient populations (Berben et al 2012; Denhaerynck et al 2018).
Author's Note:
Thank you for mentioning this important aspect. Indeed there is a wide array of factors that previously have been associated with non-adherence which exceed the personal manageability of each patient. However, due to the study design which is based on a single-center data acquisition, comparisons between different macro and meso levels unfortunately are not possible. Large-scale multi-center studies are necessary to replicate and expand our results in the future. We restricted our study to the micro or patient-level, respectively. One of our study aims is to identify patient-related factors that can be targeted in interventions, whereas factors macro and meso levels need different approaches. The choice of examined patient-related factors and thus the theoretical framework results from a thorough literature search to design the study as comprising as possible.

Reviewer:
The range of magnitude of NA in the background needs comment that this range is influenced by variability in measurement methods, operational definitions and case finding methods.
Author's Note:
As recommended we inserted the proposed explanation for a high variability in NA rates (line 54).

Method:

Reviewer:
A sample of 50 heart transplant recipients will be included with varying post-transplant follow-up. Given the large number of variables included (>25), the power for data analysis will be limited. Will it be possible to reach the aims of this prospective cohort given this major limitation.
Author's Note:
Thank you for displaying your concern and we are well aware of a potentially limited sample size. Although we are still recruiting and the definite number is not set yet, we unfortunately will not be able to extend this sample infinitely. However, our sample should suffice for the research questions we are planning to examine. Our first research questions mostly will be investigated by applying correlational

analyses as well as linear regressions which do not require power analyses. For the first RQ we are only interested in the measurement methods as potential predictors for EM, which limits the number of independent variables applied to 3. For the second RQ, we must use preliminary analyses in order to insert only the variables that are significantly correlated with the outcome. For RQ 3 we will only have the 6 variables measuring lifestyle behaviors, which again limits the number of factors inserted in the calculation. Bonferroni holm adjustments will be made for all statistical tests to correct for the alpha-error.

Reviewers:
The operational definitions of medication adherence need to be reported for each medication adherence measurement and related analysis methods need to be specified.
Author's Note:
Thank you for this recommendation.
For collateral report we included literature that used the same measurement method. We further added that it's the physician's "subjective estimate of global adherence". (line 160)
Since we used the validated instrument BAASIS to assess self-reported NA, we did not add additional information.
To define IS trough level variability we displayed in detail how it will be calculated and operationalized (line 172f.)
In line 195 we added information for electronic monitoring concerning the calculation of results and its definition (see also below).
As far as the respective analysis methods are concerned, we added additional information in the section "Statistical Analysis Plan". Also which analyses will be used for the respective research questions.

Reviewer:
The expected response rate of 50% seems very low taking other numbers for similar studies into consideration.
Author's note:
Indeed, similar studies showed higher rates. However, our expected response rate of 50% is based on our current response rate. We set the expected response rate rather conservatively so that participant number will not be overestimated. Of course we would welcome a higher number of participants.

Reviewer:
The most recent BAASIS version does not include the VAS scale as this part of the questionnaire is conceptually not appropriate (initiation/implementation/persistence) and also did not perform well in psychometric analysis. The VAS scale is therefore not recommended.
Author's Note:
Thank you for your note. Indeed the VAS is not part of the current BAASIS, however, since we planned to examine the concordance of measurement methods, we decided that the VAS could be included as well and might show interesting results. Especially since physician's estimates are also based on a similar scale in our study, comparability of these two measures is provided this way. If you have further concerns about this, we are also willing to exclude the VAS from our analyses.

Reviewer:
More details on the use of assay as adherence measure in light of the various immunosuppressive regimens used should be given. Operational definition and analysis methods for different regimens and combination of these different methods should be given.
Author's Note:
We have added some more information that the different IS regimens will be dealt with equally as far as the IS trough level variability and its calculation and analysis is concerned. Since the different IS

regimens as well as their combinations have different target levels we have displayed the IS regimens with their respective target levels in attachment file 3. We have further added the mode of analysis and calculation of the IS trough level variability. (line 181).
Reviewer:
Especially for electronic monitoring limited information is provided and the investigators are encouraged to used state of the art methods for EM analysis. How will you deal with different dosing regimens to determine operational definitions and how will you analyse your data?
Author's Note:
As already mentioned above we added some additional information as to how to process data of electronic monitoring (line 195). In order to consider different dosing regimens (once daily vs twice daily), we will calculate percentage frequencies, as was also done in Foster et al., 2018 in order to attain comparability between patients. In order to analyze potential risk factors, for example, the percentage frequency of electronically monitored NA will be used as the dependent variable (see line 222).

Discussion:

Reviewer:
Novelty of study is questioned. See comments and references above. The authors are encouraged to do a careful literature review and to argue how their single center study limited to 50 subjects can close a gap in the literature.
Author's note:
Thank you for your thorough review and your detailed suggestions. There is a great amount on literature on the subject of adherence in HTRs. We also have inserted as much additional literature as possible in the background, also according to your previous comments. However, as far as we know, especially the combination of EM with lifestyle habits and risk factors for NA is fairly new in HTRs, compared to other solid organ recipients. Indeed, a number of 50 is limited. So we would recommend to replicate this study with a bigger sample in the future.

Ethics and dissemination:

Reviewer:
There is no information, whether the patient data will be treated anonymous / pseudonymized and who will have access to the data. This should be added.
Author's Note:
We added information on pseudonymization and data access.

Reviewer:
Informed consent material is missing and should be attached in the appendix.
Author's note:
All material handed out to the patients at study enrollment will be attached (attachment file 1-2).

Further changes:
- We updated the current status of recruitment (number of participants, sociodemographic data of participants) line 233
- We further made some slight alterations according to the EMERGE guidelines (title, abstract, method section)

If further changes are necessary please do not hesitate to let us know.

VERSION 2 – REVIEW

REVIEWER	Claire Villeneuve Limoges University Hospital
REVIEW RETURNED	05-Jun-2020

GENERAL COMMENTS	Responses to reviewers' comments are well taken into account and help clarify the paper. Thank you for the additional corrections and explanation. The whole paper is much improved and can make a significant contribution to the literature. I have a couple of remaining suggestions about statistical analysis. Although the author response precisely to the reviewers answers, that was not translate into the manuscript. For example, the use of Bonferroni holm adjustments for all statistical tests to correct for the alpha-error of multiple testing (not mentioned) or, the use of Cohen's kappa and the Intraclass Correlation Coefficient for research question one. Why is it not explained in the text. This could clarify the statistical analysis plan and show that you are aware of the limited sample size and the potentially limited power of the analysis.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Claire Villeneuve

Reviewer:

I have a couple of remaining suggestions about statistical analysis. Although the author response precisely to the reviewers answers, that was not translate into the manuscript. For example, the use of Bonferroni holm adjustments for all statistical tests to correct for the alpha-error of multiple testing (not mentioned) or, the use of Cohen's kappa and the Intraclass Correlation Coefficient for research question one. Why is it not explained in the text. This could clarify the statistical analysis plan and show that you are aware of the limited sample size and the potentially limited power of the analysis.

Author:

Thank you for your recommendations. As suggested, we mentioned the intended Bonferroni-Holm Correction in the Statistical Analysis Plan (line 234). The use of Cohen's Kappa and the Intraclass Correlation Coefficient for research question (RQ) 1 is mentioned in line 224-226. Each research questions that we intend to examine is indicated in brackets after the description of the respective statistical method.

Example: "For prospective analyses, we will perform multiple linear regressions with the percentage frequency of electronically monitored NA as the outcome variable (RQ 1 and 2)."

We further inserted an explanation on how we would proceed in case of restricted predictor count due to our limited sample size (see line 232) in order to exemplify that we are aware of potential statistical limitations.

If you have further recommendations or improvements, we would appreciate if you let us know.